Memoranda

The mononuclear phagocyte system: a new classification of macrophages, monocytes, and their precursor cells*

R. VAN FURTH,[1] Z. A. COHN,[2] J. G. HIRSCH,[2] J. H. HUMPHREY,[3] W. G. SPECTOR,[4] & H. L. LANGEVOORT[5]

There have been many attempts in the past to classify phagocytic mononuclear cells and to define the cell system they are considered to form—among these being the " macrophage system " of Metchnikoff, the " reticulo-endothelial system " of Aschoff, and the " reticulo-histiocyte system " proposed by Volterra and reintroduced by Thomas. None of these is entirely adequate in the light of present knowledge. In 1969, therefore, a group of workers proposed a new classification of all highly *phagocytic mononuclear cells and their precursors in what they termed the " mononuclear phagocyte system ". This system includes the promonocytes and their precursors in the bone marrow, the monocytes in the peripheral blood, and the macrophages in the tissues. Subsequent consultation with numerous other specialists throughout the world led to a certain number of changes in this classification, which is now proposed in revised form.*

Inclusion of cells in the " mononuclear phagocyte system " is based on similarities in the morphology, function, origin, and kinetics of the phagocytes. By these criteria reticular cells, dendritic cells, endothelial cells, and fibroblasts (fibrocytes) are excluded. The proponents point out that as new knowledge is acquired modifications may have to be made, certain cells being added to or removed from the new classification.

The phagocytic cells, which play an important role in the host defence mechanism, fall into two categories: the polymorphonuclear phagocytes (granulocytes) and the mononuclear phagocytes. The mononuclear phagocytes include the tissue macrophages, the circulating monocytes, the promonocytes, and their precursor cells in the bone marrow.

Tissue macrophages are widely distributed in the body, being present in organs (e.g., the liver, spleen, lymph nodes, lungs, bone marrow, bone tissue, and nervous system), in the connective tissue, and in the serous cavities. The function of these cells is to clear the blood, lymph, and tissues of particles—for instance, microorganisms or effete cells—that are ingested by phagocytosis. This process is non-specific, and the uptake of microscopic particles is influenced by both intrinsic and external factors (Rabinovitch, 1968, 1970). After the ingestion of particulate material, enzymes are transferred to the phagocytic vacuole to break down the ingested matter. Some materials are degraded completely, but other substances may at least partially escape degradation and be retained by the cell in a form that increases its ability to stimulate immunologically competent lymphocytes (Fishman & Adler, 1967, 1970; Askonas & Jarošková, 1970; Globerson & Feldman, 1970; Unanue & Cerottini, 1970).

Cells sharing a common origin, morphology, and function may be considered as belonging to a single entity and as constituting a " system " (Aschoff,

* A French version of this paper will appear in a future issue of the *Bulletin*.

[1] Department of Microbial Diseases, University Hospital, Leiden, Netherlands.

[2] Rockefeller University, New York, N.Y., USA.

[3] National Institute for Medical Research, Mill Hill, London, England.

[4] Histopathology Department, St Bartholomew's Hospital, London, England.

[5] Department of Histology, Free University, Amsterdam, Netherlands.

1924). Cells belonging to one system are usually localized in more than one morphological compartment. Depending on their stage of differentiation and their localization in the body at a given moment, the cells of a cell system may differ qualitatively and quantitatively in their morphological and functional characteristics.

In the past many attempts have been made to define the system formed by phagocytic cells. Metchnikoff (1892) was the first to classify these cells as " macrophages " (large eaters) and " microphages " (i.e., a smaller type of phagocytic cell, the polymorphonuclear leucocyte). He demonstrated that both these types of phagocyte, which were thought to be simply scavengers, also played an important role in the host's resistance against infections, because they not only engulf but also rapidly kill and digest most of the invading microorganisms. Metchnikoff concluded that infections occurred when microorganisms resisted engulfment or were able to survive in the cytoplasm of the phagocytes. He even recognized the close relationship between the mononuclear phagocytic cells in the spleen, lymph nodes, and bone marrow, and the macrophages outside these organs—e.g., in the connective tissue. This led him to introduce the term " macrophage system ".

Aschoff (1924) developed this concept further, and grouped several kinds of cell in what he called the reticuloendothelial system. This is the term most generally used today. The cells distinguished by Aschoff, ranked in increasing order of phagocytic activity, are shown in Table 1.

Because of their very low phagocytic activity, Aschoff deliberately excluded endothelial cells and fibrocytes from the reticuloendothelial system. The reticular cells of the spleen and lymph nodes and the reticuloendothelial cells of lymph and blood sinuses constituted the reticuloendothelial system in a strict sense and, taken together with the histiocytes and the splenocytes and monocytes—which he considered to originate from histiocytes and reticuloendothelial cells—formed the reticuloendothelial system in a wider sense. In his review he makes the point that the proposal of such a system does not imply that all the cells are identical. Indeed, they differ in their morphology, arrangement, and rate of uptake of foreign materials. He indicated the importance of a certain fundamental resemblance with respect to phagocytosis and storage (*Speicherung*). These similarities do not amount to identity, but to demand complete identity would be to exclude the concept of a cell system. Aschoff expected that future research would make it possible to distinguish between these cells more accurately.

The concept of the reticuloendothelial system has been widely criticized. Maximow (1927) considered the term " reticuloendothelium " inappropriate, because the true vascular endothelial cell is morphologically and functionally very different from the histiocyte and even more so from the reticular cells. These cells do not constitute a single cell lineage and they also differ functionally. For example, the so-called clearance of the blood stream is mainly done by macrophages of the liver (Kupffer cells) and by macrophages of the red pulp of the spleen (Stiffel et al., 1970), but not by endothelial cells or reticular cells. It is therefore improper to use the terms " reticuloendothelial system " and " reticuloendothelial cells ".

The uptake of vital dye, which Aschoff used to define the reticuloendothelial system, was thought by him to result from phagocytosis. However, poorly phagocytic cells (e.g., endothelial cells, fibrocytes, reticular cells—Table 1) can also become labelled as a result of pinocytosis, especially when large amounts of dye are applied. Such labelling is therefore unreliable as a criterion for the identification of mononuclear phagocytes (Aschoff, 1924).

Table 1. The reticuloendothelial system (RES) of Aschoff

Increase of phagocytic activity ↓	Endothelial cells		RES in a wider sense
	Fibrocytes		
	Reticular cells of spleen and lymph nodes	RES in a strict sense	
	Reticuloendothelial cells of lymph and blood sinuses, including Kupffer cells		
	Histiocytes		
	Splenocytes and monocytes		

For the study of the relationship between phagocytic cells at different anatomical sites, particulate markers, which are endocytized but not digested (e.g., colloidal carbon, polystyrene latex particles, iron oxide, and colloidal gold), are also unreliable. If such markers are released from the initially labelled cells, for example after death of the cell, these materials might be taken up by other cells with a high or low endocytic activity.

Thomas (1949) remarked that the often criticized term " reticuloendothelial system ", used " especially by pathologists and immunologists ", had become more objectionable. He reintroduced the term " reticulohistiocyte system ", which had been proposed by Volterra as early as 1927. According to Thomas, the *état histiocytaire* is not limited to the histiocytes of the connective tissue, since it can also be adopted by other cells such as striated and smooth muscle cells, bone cells, Schwann cells, and epithelial cells, all of which can acquire the " histiocytic state " under special circumstances. Among the functional properties of these cells Thomas included not only phagocytosis and motility but also enhanced metabolic activity, for instance, a high rate of protein synthesis, which was considered essential for proliferation and cell growth. Once established, he argued, the histiocytic state was stable; active histiocytes could become resting histiocytes or reticular cells.

Neither the concept of the reticuloendothelial system nor that of the reticulohistiocyte system provides a fully satisfactory framework into which the present knowledge of phagocytic mononuclear cells can be fitted. For that reason, during a conference on mononuclear phagocytes held in Leiden, The Netherlands, in 1969, a new classification of these cells was proposed by a committee and put forward for discussion during the meetings.[1] Later, after consultation among other specialists in this field, some changes were made, and these have been incorporated into this paper.

Current knowledge concerning their morphology, function, and kinetics makes it possible to place all *highly* phagocytic mononuclear cells and their precursors in one system. It is recommended that this system be called the " mononuclear phagocyte system " (MPS).

The morphology of the mononuclear phagocytes is to some extent dependent on the organ or tissue in which they are present. For normal animals, the most specific morphological characteristics of these cells, localized in the bone marrow, circulation, or tissues (Sutton & Weiss, 1966; Hirsch & Fedorko, 1970; Robineaux et al., 1971; Nichols et al., 1971) are summarized in Table 2.

By structural criteria alone the mononuclear phagocytes are sometimes hard to distinguish from lymphocytes. However, the lymphocytes belong to a different cell lineage, by reason of their different origin (thymus and bone marrow), life span (short- and long-lived), and function (e.g., nonphagocytic) (Craddock et al., 1971). The term " mononuclear cells ", frequently used to designate lymphocytes, monocytes, and macrophages, is inadequate; it does not properly characterize these cells with respect to their function, life history, and morphology.

The functional criteria justifying the inclusion of the macrophages, monocytes, and promonocytes in a single system are avid phagocytosis and pinocytosis, especially the former, as well as the ability to attach firmly to a glass surface (Table 2) (Rabinovitch, 1968, 1970; Cohn, 1968, 1970). These properties provide a means for the characterization and isolation of these cells. The process of particle uptake by mononuclear phagocytes can be divided into two discrete phases: first attachment of the particle to the cell surface, and then ingestion. Monocytes and macrophages have receptor sites for immunoglobulins and complement at the cell surface (Berken & Benacerraf, 1966; Lay & Nussenzweig, 1968, 1969; Nelson, 1969; Huber & Fudenberg, 1970). The attachment of particles is mediated by antibodies (against the particles) or by antibodies and complement. Attachment can also be facilitated by other factors present in normal sera, which in some instances have been identified as immunoglobulins but in others are still unidentified. Some kinds of particle might become attached without apparent need for serum factors. Phagocytosis mediated by immunoglobulins with or without complement is termed " immune " phagocytosis. The monocytes and macrophages, which carry immunoglobulin and complement receptors at the cell surface, may be regarded as " professional " phagocytes (Rabinovitch, 1967), to distinguish them from " facultative " (" nonprofessional ") phagocytic cells. The latter cells (e.g., fibroblasts, reticular cells, and endothelial cells), which can ingest particles at a low rate and independently of immunoglobulins or complement, probably do not have receptors for these components. Phagocytosis by some of the facultative phagocytic cells is

[1] The initial version of this proposal is included in the conference proceedings (Langevoort et al., 1970).

Table 2. Characteristics of normal mononuclear phagocytes

Characteristic [a]	Bone marrow promonocytes	Peripheral blood monocytes	Tissues	
			Free macrophages	Fixed macrophages
Cell diameter	14–20 μm	10–14 μm	10–25 μm	
Nuclear/cytoplasmic ratio	⩾1	∾1	<1	<1
Nucleus				
shape	folded or indented	reniform	reniform or oval	reniform or oval
nucleoli	+	+	+	+
DNA synthesis	50–70%	0–1%	0.5–3%	1.5–2.5%
Cytoplasm				
polyribosomes	+++	+	±	±
endoplasmic reticulum	+	+	++	++
Golgi complex	large	smaller	variable size	variable size
mitochondria	++	++	++ to +++	++ to +++
lysosomes	+	+	++ to ++++	++ to ++++
endocytic vesicles	+	+	++ to ++++	++ to ++++
Surface membrane				
ruffling	++	+++	++++	
microvilli	+	++	+++	+++
Functional properties				
adherence to glass	+++	+++	+++ to ++++	
pinocytosis	+	++	+++	+++
immune phagocytosis	++	+++	++++	++++

[a] The greater the number of plus signs shown against each characteristic, the greater its degree or frequency.

even inhibited by serum, probably by masking of the sites of interaction between the particles and the cell surface (Rabinovitch, 1970).

In addition to morphological and functional characteristics, the results of cytokinetic studies (van Furth, 1970a, 1970b; Volkman, 1970; Spector & Ryan, 1970; Roser, 1970) also provide cogent reasons for proposing the " mononuclear phagocyte system ". These studies were carried out in normal animals, in animals with an acute or chronic inflammation, in lethally irradiated animals with or without bone marrow shielding, in radiation chimaeras, and in parabiotic animals, using radioactive isotopes, chromosomes, or tissue antigens as stable markers to trace the cells. These studies have demonstrated conclusively that mononuclear phagocytes originate from precursor cells in the bone marrow, are transported *via* the peripheral blood as monocytes, and eventually become tissue macrophages. Ontogenetic studies have provided additional evidence for this, since mononuclear phagocytes do not appear in tissue until it has been vascularized (Andersen & Matthiesen, 1966). Normally, tissue macrophages seem to undergo a continuous slow turnover and to divide infrequently (Table 2) (van Furth, 1970b). Under pathological conditions, macrophages at the inflammatory lesion still arise from blood monocytes, but local multiplication of macrophages may also occur (Spector & Ryan, 1970; North, 1969). Cytokinetic studies have not provided

any evidence that mononuclear phagocytes are derived from lymphocytes.

The proposed concept of a mononuclear phagocyte system, comprising a group of cells that are related by similarities of morphology, function, and origin, is more coherent than either the reticuloendothelial system or the reticulohistiocyte system. The term " mononuclear phagocyte ", already used by Metchnikoff as early as 1892, is considered to be the most appropriate to designate the entire cell line. Although polymorphonuclear phagocytes are mononuclear too, they belong to another cell line because of their different origin and divergent kinetic and functional behaviour.

On the basis of the criteria discussed above, the mononuclear phagocytic system can be defined as shown in Table 3.

The most immature cell of the mononuclear phagocyte system, which can be recognized in the bone marrow, is the promonocyte. This is a multiplicative cell (Table 2) that by dividing gives rise to two monocytes. Although the promonocyte is the earliest identifiable cell in this system, there must be a more immature precursor cell feeding into the pool of promonocytes (van Furth & Diesselhoff-Den Dulk, 1970). Monocytes in the circulation constitute a mobile pool of relatively immature cells on their way from the place of origin to the tissues (van Furth, 1970a, 1970b; Volkman, 1970). At sites where conditions are favourable for phagocytosis, these cells become macrophages and will acquire the necessary equipment for the digestion of phagocytized material. It is at this stage, usually in the extravascular compartment, that the mononuclear phagocytes are avidly phagocytic.

Table 3. The mononuclear phagocyte system

Cells	Localization
PRECURSOR CELLS	bone marrow
↓	
PROMONOCYTES	bone marrow
↓	
MONOCYTES	bone marrow, blood
↓	
MACROPHAGES	connective tissue (histiocytes) liver (Kupffer cells) lung (alveolar macrophages) spleen (free and fixed macrophages) lymph node (free and fixed macrophages) bone marrow (macrophages) serous cavity (pleural and peritoneal macrophages) bone tissue (osteoclasts?) nervous system (microglial cells?)

Since the early studies by Florey and others (for a review, see Florey, 1970), it has been established that, under both normal and pathological conditions, macrophages of connective tissues (histiocytes) and of serous cavities (e.g., peritoneal and pleural macrophages) are derived from peripheral blood monocytes.

The monocytic origin has also been demonstrated for macrophages in many different organs (see review of kinetic data in van Furth, 1970a, 1970b). Recent kinetic studies have shown this origin for the macrophages in the liver (Kupffer cells) and in the lung (alveolar macrophages). Chimaera studies have demonstrated the bone-marrow origin of liver, lung, spleen, and peritoneal macrophages (Balner, 1963; Goodman, 1964; Pinket et al., 1966; Virolainen, 1968; Howard, 1970, Godleski & Brain, 1972; Shand & Bell, 1972). The reported exception—namely, that, in the unusual situation of the proliferative phase of the allogeneic graft-*versus*-host reaction, the macrophages of the liver, lung, and peritoneal cavity originate from thoracic duct lymphocytes (Howard, 1970)—has not been found in xenogeneic chimaeras (Bell & Shand, 1971).

In the spleen, lymph nodes, and bone marrow, the free macrophages are derived from monocytes. The fixed macrophages in these organs are probably also of monocytic origin, but definitive proof on this point has not yet been obtained. However, the morphology and functional behaviour of the fixed macrophages justify their inclusion in the mononuclear phagocyte system. In the spleen and lymph nodes, both free and fixed macrophages occur in close association with the reticular cells, the free macrophages lying in the interstices of the framework composed of reticular cells, and the fixed macrophages being attached to cytoplasmic extensions of the reticular cells. Fixed macrophages, unlike the reticular cells, have never been found to form reticulin fibres (Ross, 1968).

Since there is reliable evidence that the phagocytic cell of the bone, i.e., the multinucleated osteoclast, may arise by coalescence of monocytes, these cells are included in the proposed system (Hancox, 1956; Jee & Nolan, 1962; Fischman & Hay, 1962; Andersen & Matthiessen, 1966; Gieseking, 1966; see also Ham, 1969). With less certainty, the phagocytic cell of the nervous system (microglial cell) is also

included (Dunning & Furth, 1935; Russell, 1962; see also Ham, 1969). Evidence for the probable derivation of this cell from the blood monocyte is afforded by two facts: during the development of the central nervous system, microglial cells are found only after the blood vessels have grown in (Andersen & Matthiessen, 1966); and in pathological processes the accumulated mononuclear phagocytes originate from circulating monocytes (Kosunen et al., 1963; Koningsmark & Sidman, 1963; Waksman, 1965; Huntington & Terry, 1966).

In inflammatory reactions giant cells can be found; these multinucleated cells also belong to this system, because they are formed by the fusion of mononuclear phagocytes. The epithelioid cells occurring in these lesions also arise from monocytes or macrophages (Sutton & Weiss, 1966; Papadimitriou & Spector, 1971; see also Florey, 1970).

The reticular cells themselves are not regarded as mononuclear phagocytes, because, even though they can ingest particulate materials, they are not highly phagocytic (Weiss, 1964), and since they do not show immune phagocytosis (Stuart & Davidson, 1970) they may lack receptors for immunoglobulins. Furthermore, these cells do not have the same ancestors as macrophages. For similar reasons, the dendritic cells in the follicles of the spleen and lymph nodes, although they can retain antigen macromolecules at the surface of their dendritic cytoplasmic extensions, are considered, in the light of present knowledge, not to belong to the mononuclear phagocyte system (White, 1963; Nossal et al., 1968).

The endothelial cell (Payling Wright, 1970; see also Carr, 1970, and Florey, 1970) and the fibroblast (syn. fibrocyte) (Grillo, 1963, 1964; Gieseking, 1963; Ross et al., 1970) are definitely excluded from the mononuclear phagocyte system. Both these cell types lack the morphological characteristics of mononuclear phagocytes; neither originates from peripheral blood monocytes; and neither is highly phagocytic.

Some of the cells classified as macrophages and included in this system have not yet been studied sufficiently for all the stipulated criteria to be satisfied. Consequently, new knowledge may require that certain cells be removed from or others added to the group of macrophages. Nevertheless, the present classification of the mononuclear phagocytes in one system has the advantage of simplicity and can contribute to the understanding of the behaviour of the mononuclear phagocytes in physiological and pathological conditions.

ACKNOWLEDGEMENTS

This paper is based on a proposal made by the authors at the Conference on Mononuclear Phagocytes, Leiden, 2–5 September 1969. The version presented here was agreed upon following modification of the original proposal by the authors and by the following scientists: A. C. Allison, UK; G. L. Asherson, UK; Brigitte Askonas, UK; Dorothy F. Bainton, USA; B. Benacerraf, USA; E. Benditt, USA; D. H. Bowden, Canada; S. Bozsoky, Hungary; G. Brondz, USSR; I. Carr, UK; H. Cottier, Switzerland; A. M. Dannenberg, USA; J. R. David, USA; N. B. Everett, USA; Astrid Fagraeus, Sweden; R. M. Fauve, France; D. W. Fawcett, USA; J. Feldman, USA; M. Feldman, Israel; H. Fischer, Federal Republic of Germany; M. Fishman, USA; T. M. Fliedner, Federal Republic of Germany; H. H. Fudenberg, USA; E. R. Gabrieli, USA; P. R. Glade, USA; Amiela Globerson, Israel; L. E. Glynn, UK; R. A. Good, USA; J. G. Hall, UK; B. Halpern, France; M. Hanaoka, Japan; M. Holub, Czechoslovakia; J. G. Howard, UK; B. D. Janković, Yugoslavia; K. Kageyama, Japan; M. L. Karnowski, USA; F. J. Keuning, Netherlands; S. J. Klebanoff, USA; D. Korn, USA; G. B. Mackaness, USA; G. Majno, Switzerland; O. Mäkëla, Finland; G. Mathé, France; D. Metcalf, Australia; J. F. A. P. Miller, Australia; P. G. Munder, Federal Republic of Germany; Q. N. Myrvik, USA; D. S. Nelson, Australia; R. J. North, USA; G. V. J. Nossal, Australia; A. B. Novikoff, USA; V. Nussenzweig, USA; G. O'Conor, USA; R. D. Perez Tamayo, Mexico; B. Pernis, Italy; M. Rabinovitch, USA; B. Roser, Australia; R. Ross, USA; M. Seligmann, France; M. Simonsen, Denmark; E. Sorkin, Switzerland; J. Sterzl, Czechoslovakia; Jeannette Thorbecke, USA; E. R. Unanue, USA; M. Virolainen, Finland; A. Volkman, USA; P. Ward, USA; D. M. Weir, UK; R. S. Weiser, USA; B. Waksman, USA; R. G. White, UK; M. M. Wintrobe, USA; D. Zucker-Franklin, USA.

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